# APPLICATION OF THE JAPP-KLINGEMANN REACTION TO THE PREPARATION OF α-ACYL PYRIDINES

BY

ROBERT RICHARD PHILLIPS

A.B., Central College, 1942
A.M., University of Illinois, 1947

## AN ABSTRACT OF A THESIS

SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS
FOR THE DEGREE OF DOCTOR OF PHILOSOPHY IN CHEMISTRY
IN THE GRADUATE COLLEGE OF THE
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# APPLICATION OF THE JAPP-KLINGEMANN REACTION TO THE PREPARATION OF α-ACYL PYRIDINES

## Introduction

Previous syntheses of 2-acylpyridines have been by the pyrolysis of mixtures of calcium salts of picolinic and aliphatic acids (1), by the condensation of ethyl picolinate and ethyl acetate followed by hydrolysis and decarboxylation (2), and by the reaction of a Grignard reagent with 2-cyanopyridine (3). Other special methods for synthesizing 2-formylpyridine are known, but they are restricted to that one member of the series.

Of the three methods mentioned above only the first has been found to be applicable to 2-propionylpyridine and the higher homologs. The desire for a better and more general synthesis was the starting point for this research problem.

It was thought that the Japp-Klingemann reaction (4) might be applied to 2-pyridylacetic acid derivatives and thus lead to phenylhydrazones of the desired ketones. This would constitute a new application of this type reaction, as it had been previously restricted to α-ketoacetic acid type reactants.

## Discussion Of Results

The 2-pyridylacetic acid derivatives necessary as reactants for the diazonium salts were prepared by three successful methods, while one other method was found to fail.

Condensation of ethyl oxalate with 2-picoline in the presence of potassium ethoxide could not be effected, although such a condensation has been successful with quinaldine (5).

The Willgerodt reaction on 2-vinylpyridine (6) produced 2-pyridylacetamide in yields of 25-30 per cent of the theoretical amount. Inability to convert this amide to an ester in order that the methylene group could be alkylated as required for

2-acetylpyridine and its higher homologs made this preparation impractical.

Reaction of 2-picolyllithium (7) with carbon dioxide and subsequent esterification produced ethyl 2-pyridylacetate in amounts of 25 per cent based on lithium. Alkylation to obtain the higher homologs again is unsatisfactory, as quaternization of the tertiary nitrogen atom is an important side reaction. Substitution of a lithium atom on the *alpha* carbon atom of 2-ethylpyridine and subsequent reaction with carbon dioxide and esterification could be a means of avoiding the alkylation step, but such an attempted synthesis produced only traces of the desired ester.

Condensation of 2-bromopyridine with 5-alkylated barbituric acids followed by hydrolysis and decarboxylation led to alkylated 2-pyridylacetic acid salts. In this manner *n*-propyl and *n*-butyl-2-pyridylacetic acid salts were synthesized.

The Japp-Klingemann reaction was found to work well on the hydrolyzed 2-pyridylacetamide, on the hydrolyzed ethyl 2-pyridylacetate, and on the acidified salts produced by the barbituric acid route. Comparison of results using sulfanilic acid, *p*-nitroaniline, and *p*-aminobenzoic acid as the amines for diazotization and subsequent reaction with hydrolyzed ethyl 2- pyridylacetate showed that *p*-aminobenzoic acid gave quantitative yields of almost pure *p*-carboxyphenylhydrazones, while the others gave lesser yields but in no case less than 65 per cent of the theoretical amount.

Conversion of the *p*-carboxyphenylhydrazone of 2-butyrylpyridine to the free ketone was accomplished to the extent of 80 per cent by an interchange reaction with pyruvic acid. Thus the over-all yield of 2-butyrylpyridine as derived through the condensation of 2-bromopyridine with 5-*n*-propylbarbituric acid, hydrolysis and decarboxylation of this disubstituted barbituric acid, the Japp-Klingemann reaction, and interchange of the resulting *p*-carboxyphenylhydrazone with pyruvic acid was 25 per cent based on the monosubstituted barbituric acid or 60 per cent based on the disubstituted

product.

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## VITA

The author was born in Fayette, Missouri, on September 2, 1920. He attended public schools in Fayette, Missouri, and Jefferson City, Missouri, and was graduated from Jefferson City Public High School in May, 1938. He entered Central College in September, 1938, and received his Bachelor of Arts degree from that institution in June, 1942. He was employed by the Eastman Kodak Company, Rochester, New York, until in August, 1942, he joined the United States Navy. He served as a naval aviator until put on inactive duty in December, 1945. In March, 1946, he entered the Graduate College of the University of Illinois where he received his Master of Arts degree in February, 1947. He held part-time teaching assistantships in 1946, 1947, and the summer of 1948, and also held fellowships from the Minnesota Mining and Manufacturing Company and the University of Illinois in 1948-1949.

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